

Appl. No. 09/775,046  
Amtd. Dated August 11, 2003  
Reply to Office Action of March 11, 2003

**IN THE SPECIFICATION:**

Please replace the paragraph on page 4, lines 9-13, with the following rewritten paragraph:

Figure 1 shows an alignment between various IL-1 family members. Positions refer to the alignment and are not residue numbers. ~~IL-1 $\alpha$~~  is SEQ ID NO:5, ~~IL-1 $\beta$~~  is SEQ ID NO:6, ~~IL-1RA~~ is SEQ ID NO:7, ~~mIL-1 $\gamma$~~  is SEQ ID NO:8, ~~mIL-1 $\epsilon$~~  is SEQ ID NO:9, and ~~mIL-1 $\delta$~~  is SEQ ID NO:10. hIL-1 $\alpha$  is SEQ ID NO:5; hIL-1 $\beta$  is SEQ ID NO:6; hIL-1RA is SEQ ID NO:7; mIL-1 $\gamma$  is SEQ ID NO:8; hIL-1 $\epsilon$  is SEQ ID NO:9; mIL-1 $\delta$  is SEQ ID NO:10; hIL-1 $\epsilon$  is SEQ ID NO:4; mIL-1 $\delta$  is SEQ ID NO:11; and hIL-1 $\delta$  is SEQ ID NO:2.

Please replace the paragraph beginning on page 77, line 12, and continuing to page 78, line 7, with the following rewritten paragraph:

To study whether the novel IL-1s function like the classical IL-1s, the genes were expressed and purified as adenovirus-derived human IL-1 $\delta$  and IL-1 $\epsilon$ , and tested for their capacity to initiate IL-1 signaling, with an NF $\kappa$ B reporter assay as a read-out. The observation that the classical IL-1R pairs IL-1R1/3 and IL-1R5/7 do not respond to these new protein preparations might be explained by the fact that receptor-ligand combinations within the IL-1 system are very specific. Therefore, IL-1R4 and IL-1R6 were tested in combination with various other IL-1R-like molecules. These studies consistently showed the usage of IL-1R6 by IL-1 $\epsilon$ , but not IL-1 $\delta$ , to activate NF $\kappa$ B in Jurkat cells. Even IL-1R6 single transfections showed this response. The IL-1 system, as understood today, typically requires two receptors, one ligand-binding receptor and one signaling receptor, to get an IL-1 response. Since IL-1R6 is very homologous to IL-1R1 (Lovenberg, et al. (1996) J. Neuroimmunol. 70:113-122), a ligand-binding type of receptor, it was supposed that Jurkat cells endogenously express a second

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signaling type of receptor that can pair with IL-1R6 in the presence of IL-1 $\epsilon$ . By PCT analysis, the following IL-1R-like molecules are expressed by untransfected Jurkat cells: IL-1R3, IL-1R4, IL-1R8 (e.g., SIGIRR), and IL-1R9, and IL-. Co-transfection of IL-1R6 with IL-1R3, IL-1R9, or IL-1R10 does not potentiate the response to IL-1 $\epsilon$  relative to IL-1R6 single transfectants. In addition, studies by others using IL-1R1 chimaeras and an IL-1 $\alpha$ -mediated activation of NF $\kappa$ B as a read-out do not seem to favor the combination of IL-1R6 and IL-1R8 to mediate an IL-1 response. Thomassen, et al. (1999) Cytokine 11:389-399. The search for the additional IL-1 $\epsilon$  receptor(s) is currently ongoing.

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